In the Claims

Please cancel Claims 1-8 and 11-27.

Please amend the claims as follows:

9. (Amended) An antibody that is capable of binding [the] an isolated substantially homogeneous *mpl* ligand [polypeptide of Claim 3], the *mpl* ligand consisting of amino acid residues 1 to X of Figure 8 where X is selected from the group 153, 164, 191, 205, 207, 217, 229, 245 and 332.

REMARKS

Claim 9 and 10 are in this case and have been amended to incorporate language from claims from which they depend and which have been canceled. The title has been amended to more clearly reflect the claimed subject matter. The specification has been amended to correct inadvertent typographical errors. Applicants submit no new matter has been added. Applicants respectfully request reconsideration in view of the foregoing amendments and explanation below.

Double Patenting Rejections

Applicants acknowledge the many possible double patenting rejections possible in this large family of related cases. No claims however have yet issued. However, when one does, Applicants intend to cancel claims to coextensive subject matter or file a terminal disclaimer as necessary.

Rejection under 35 USC §102(b) and 103

The Examiner has rejected the pending claims as being anticipated or in the alternative obvious over three primary references authored by McDonald.

Applicants respectfully traverse. First, there is no evidence or teaching in any of the references that McDonald has produced an antibody to the TPO antigen of Applicants' claims as amended. Second, there is no evidence in any of the references that McDonald has produced an antibody to any form of TPO -- rather only to a TPO activity. Finally, Applicants submit the Withy et al. reference which independently concludes that the source of the McDonald "TPO-like" activity was probably Erythropoietin, Interleukin-6, or TGF-β.

McDonald et al., *Proc. Soc. Exp. Biol. and Med.* 182:151-158 (1986) claim to have isolated monoclonal antibodies to human urinary thrombopoietin based on immunizing mice with a partially purified TSF(TPO)-rich preparation of human urine. This preparation is assayed for TSF or TPO activity (page 151). Thus the evidence that this urine fraction contains TPO is based on a TPO activity measurement. It is well known (see e.g., Withy et al. below) that many factors can produce TPO-like activity. These include IL-3, IL-6, IL-11 (currently in phase III clinical trials as a "TPO"), LIF and others. Thus the best that can be said regarding this "partially purified urine" is that it may contain a candidate TPO.

Evidence that these antibodies are to TPO comes from the fact that these antibodies are capable of binding a "highly purified TSF-rich preparation (10)" (see page 152, second column). Reference 10 is McDonald et al., *J. Lab. Clin. Med.* 106:162-174 (1985) (see page 158). This reference describes purification of "thrombopoietin" from human embryonic kidney (HEK) cell culture medium. Page 173 of this reference (second column) points out that this TPO (TSF) is stable to sodium dodecyl sulfate (SDS) polyacrylamide gel electrophoresis (PAGE). This is a property NOT shared with Applicants' TPO. Applicants' TPO is not stable to SDS-PAGE. Figure 1 of Applicants' specification shows TPO is unstable to heat and thiols (DTT) or mercaptoethanol.

If the McDonald TPO is not the same as Applicants' TPO, what is it and why does it have TPO-like activity? Independent evidence as to the source of TPO-like activity is provided by Withy et al. *J. Cell Physiol.* 153:362-372 (1992). These authors specifically refer to the McDonald et al. 1989 reference (see page 363, first column) and conclude that the source of megakaryopoiesis (TPO-like activity) produced in human embryonic kidney cell (HEK) culture is due to erythropoietin (EPO), interleukin-6 (IL-6) and transforming growth factor beta (TGF-β) (see page 363, top of column 2).

Thus the antibodies prepared by McDonald to a partially purified urine sample cross-react with material purified from HEK cell culture which has been independently demonstrated to be EPO, IL-6, or TRF-β.

The Examiner also refers to the McDonald et al. *Exp. Hematol.* 17:865-871 (1989) reference as rendering Applicants' antibodies obvious. Applicants direct the Examiner to page 870, third full

paragraph, where TSF (TPO) is described as stable to β-mercaptoethanol, SDS and heat. Again, this is in contrast to Applicants' TPO which is unstable to heat and thiols (DTT).

In summary, the antibodies produced by McDonald cross-react with a TPO that has different physical properties compared to Applicants'. Withy et al. suggest that this "TPO" might be EPO, IL-6, or TGF-β. Accordingly, Applicants respectfully request reconsideration of application of the McDonald et al. articles. Applicants believe the claims as amended are free of art and in condition for allowance.

Respectfully submitted,

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